Target-based drug discovery: from protein structure to small-molecules by MCR chemistry

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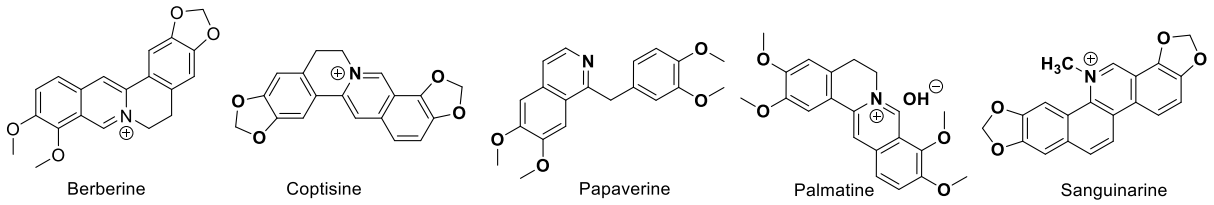
Chapter 5

Efficient and Diverse Synthesis of Isoquinoline Derivatives and Benzo[*d*]azepinone Scaffolds by New Ugi/Pomeranz–Fritsch Reaction

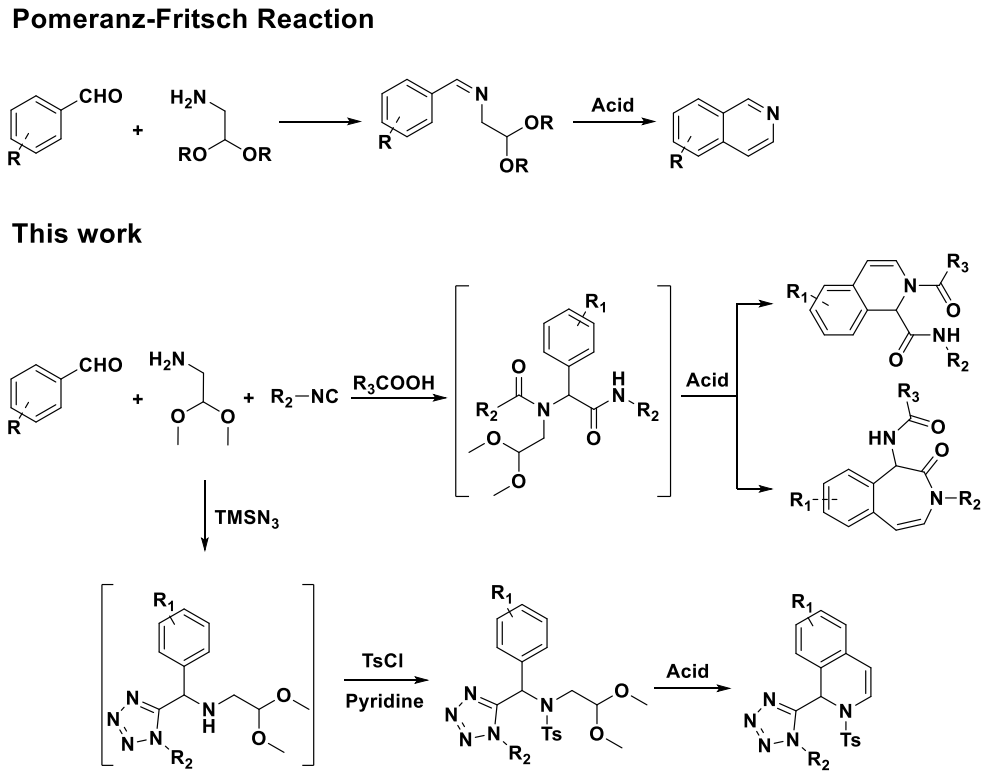
The isoquinoline represent as important heterocyclic template and privileged moiety in medicinal chemistry and exhibit a wide variety of biology and pharmacological properties.[1-6] More importantly, this scaffold make the largest family of alkaloids which have been extensively used in the history of folk medicine including berberine, coptisine, jatrorrhizine, papaverine, palmatine and sanguinarine (Scheme 1).[7-12] Considering the importance of isoquinoline, much efforts has been made toward the development of efficient methodologies to obtain this skeleton in the last century.[13-18]



Scheme 1. Examples of isoquinoline alkaloids.

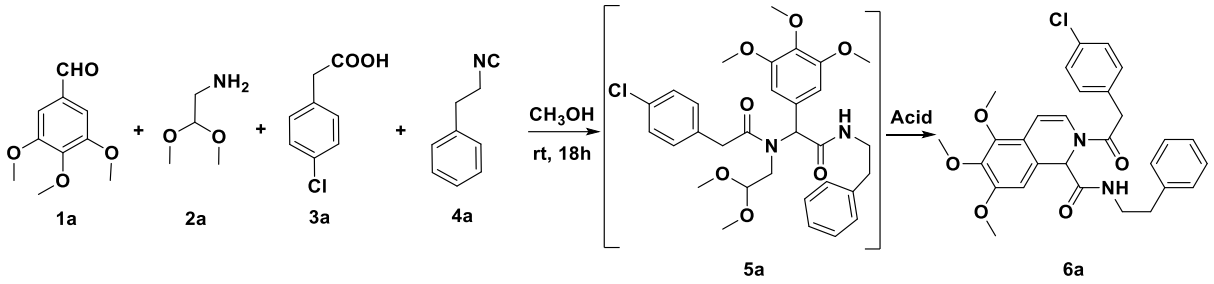
The known traditional methods to construct the isoquinoline core include the Bischler–Napieralski reaction,[19] the Pictet–Spengler reaction[20] and the Pomeranz–Fritsch reaction.[21] The Bischler–Napieralski reaction was the most frequently explored stereo-controlled isoquinoline alkaloids synthesis approach in the past decade as it creates a stereo-genic center in C1 position by a sequential reduction step. The Pictet–Spengler reaction forms the tetrahydroisoquinoline or related heterocyclic systems by condensation of a *β*-arylenylamine such as tryptamine with an aldehyde or its synthetic equivalents under acid conditions. It has not only been explored as a convenient method for the asymmetric synthesis of isoquinoline alkaloids, but also widely used for the synthesis of alkaloid-like polycyclic compounds by combining with MCR chemistry in recent years.[22-31] The Pomeranz–Fritsch reaction is the synthesis of isoquinolines via an acid-mediated electrophilic cyclization of benzalaminoacetals prepared by the condensation of benzaldehyde with electron-donating group and a 2,2-dialkoxyethylamine. Since the first and concurrent report by Pomeranz and Fritsch in 1893, this reaction has been extensively modified. [32-44] To improve the reaction yield, the Fischer modification involved the treatment of benzalaminoacetal with fuming sulfuric acid. In 1948, E. Schlittler and J. Müller modified the reaction by using benzyl amines and glyoxal semiacetal as the starting material. Later on, Bobbitt reported synthesizing the 1,2,3,4-tetrahydroisoquinolines by hydrogenation of the imine intermediate in situ to the

aminoacetal, which allows for the preparation of 1-, 4- and *N*-substituted isoquinolines. At the same time, Jackson described the dehydrogenation of 1,2-dihydroisoquinoline via a *N*-tosyl derivative to a fully aromatic system.



Scheme 2. Pomeranz–Fritsch reaction and its modifications.

Although a variety of modifications have been introduced to improve the Pomeranz–Fritsch strategy, it has not been explored as often as the Bischler–Napieralski reaction and Pictet–Spengler reaction. Only a few isolated reports on the synthesis of isoquinoline derivatives based on Pomeranz–Fritsch reaction have been published. [45-51] Inspired by the fact that the Pictet–Spengler reaction has been successfully used in the Ugi post-condensation strategy in our lab, we surmised that the combination of Ugi reaction with Pomeranz–Fritsch reaction could also be an attractive way to form diversified isoquinolines (Scheme 2).



Entry	Acid	Yield of **6a**[a] (%)
1	HCOOH	-
2	CH_3COOH	-
3	CH_3COOH/conc. H_2SO_4(v/v) = 3:1	33
4	CH_3COOH/conc. H_2SO_4(v/v) = 2:1	36
5	CH_3COOH/conc. H_2SO_4(v/v) = 1:1	30
6	CF_3COOH	46
7	37% Aq. HCl/ Dioxane(v/v) = 1:4	-
8	37% Aq. HCl/ Dioxane(v/v) = 1:2	-
9	37% Aq. HCl/ Dioxane(v/v) = 1:1	-
10	37% Aq. HCl	-
11	CH_3SO_3H (2 eq)/ CH_3CN	Traces
12	CH_3SO_3H (10 eq)/ CH_3CN	35
13	CH_3SO_3H (20 eq)/ CH_3CN	52
14	CH_3SO_3H (20 eq)/ DCM	43
15	CH_3SO_3H	15

[a] Isolated yield

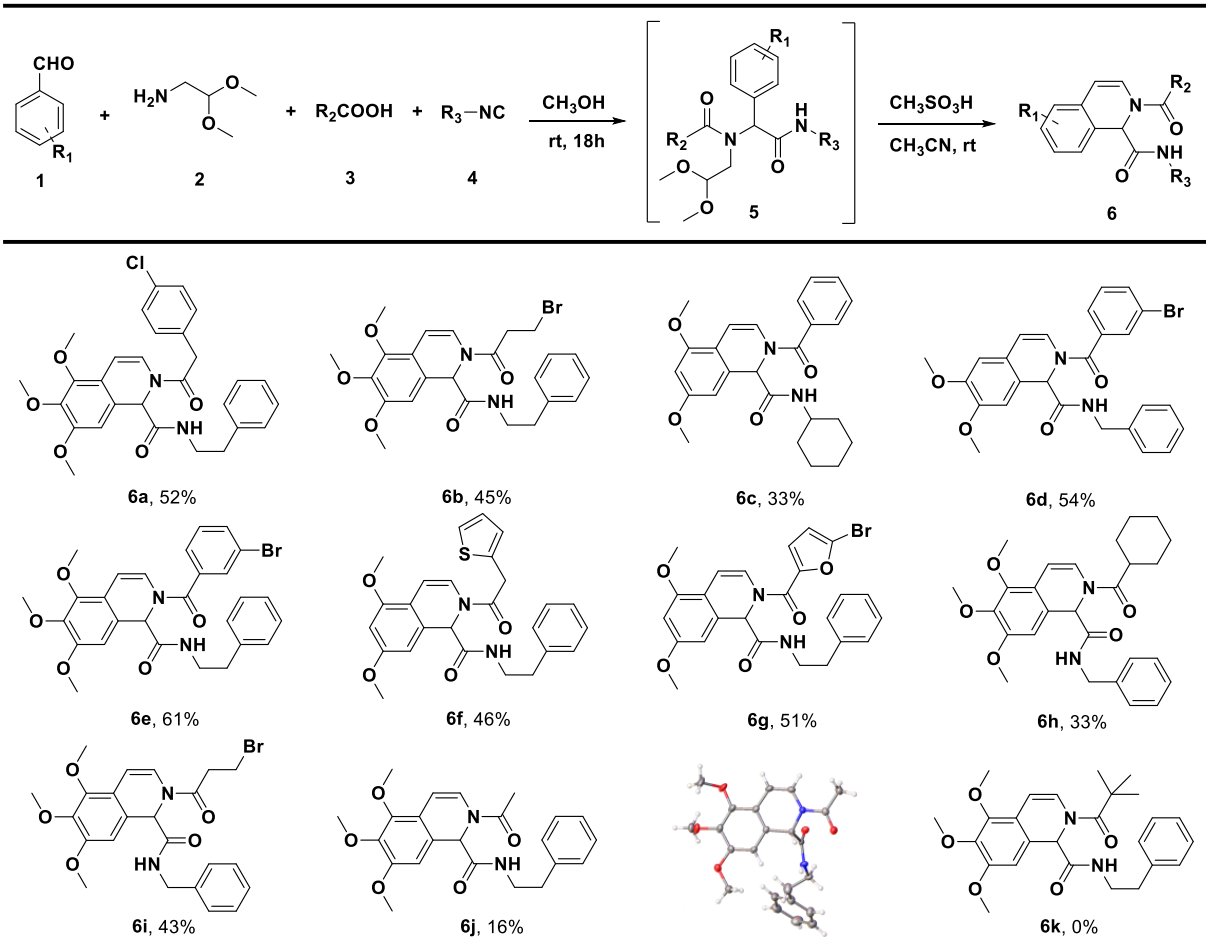
Scheme 3. Optimization of reaction conditions.

We first explored the Pomeranz–Fritsch reaction as the Post-Ugi strategy. By using 3,4,5-trimethoxybenzaldehyde, 2,2-dimethoxyethylamine, 4-chlorophenylacetic acid and phenylethyl isocyanide as test substrates, the Ugi reaction was conducted in methanol at room temperature for 18 h. As the Ugi reaction works excellently with aliphatic aldehydes and amines, the Ugi adduct **6a** was not separated but directly treated with various acids after a simple workup

(Scheme 3). It is worthy to note that Alex Nadzan and co-workers has reported the formation of 2-oxopiperazines by Ugi-*N*-acyliminium ion cyclization with good yield using TFA as acid. [52] Therefore, there is a competition between Ugi-*N*-acyliminium ion cyclization and Ugi-Pomeranz–Fritsch reaction in acid condition when the electron rich benzaldehyde is used. To our delight, no 2-oxopiperazines product was observed in all the acid conditions we screened and 46% of isoquinoline product **6a** was formed when TFA was used as the acid. However, the HCOOH, CH_3COOH, 37% HCl and 37% HCl diluted in dioxane failed to give any isoquinoline product. CH_3COOH and coc. H_2SO_4 was found to be a good combination for this reaction, which afforded **6a** in 30-36% yield. Methanesulfonic acid, which has been proved to be a good acid condition for Ugi/Pictet-sprengler reaction, also works well in our Ugi/ Pomeranz–Fritsch sequence. [53, 54] Although only traces amount of product was formed when 2 equivalent of methanesulfonic acid was used, the reaction yield increased to 35% when methanesulfonic acid increased to 10 equivalent. Finally, 20 equivalent of methanesulfonic acid in acetonitrile turned out to be the best condition for this reaction which afforded **6a** in 52% yield in two step. Replacement of acetonitrile with DCM or use methanesulfonic acid without any dilution did not further improve the reaction.

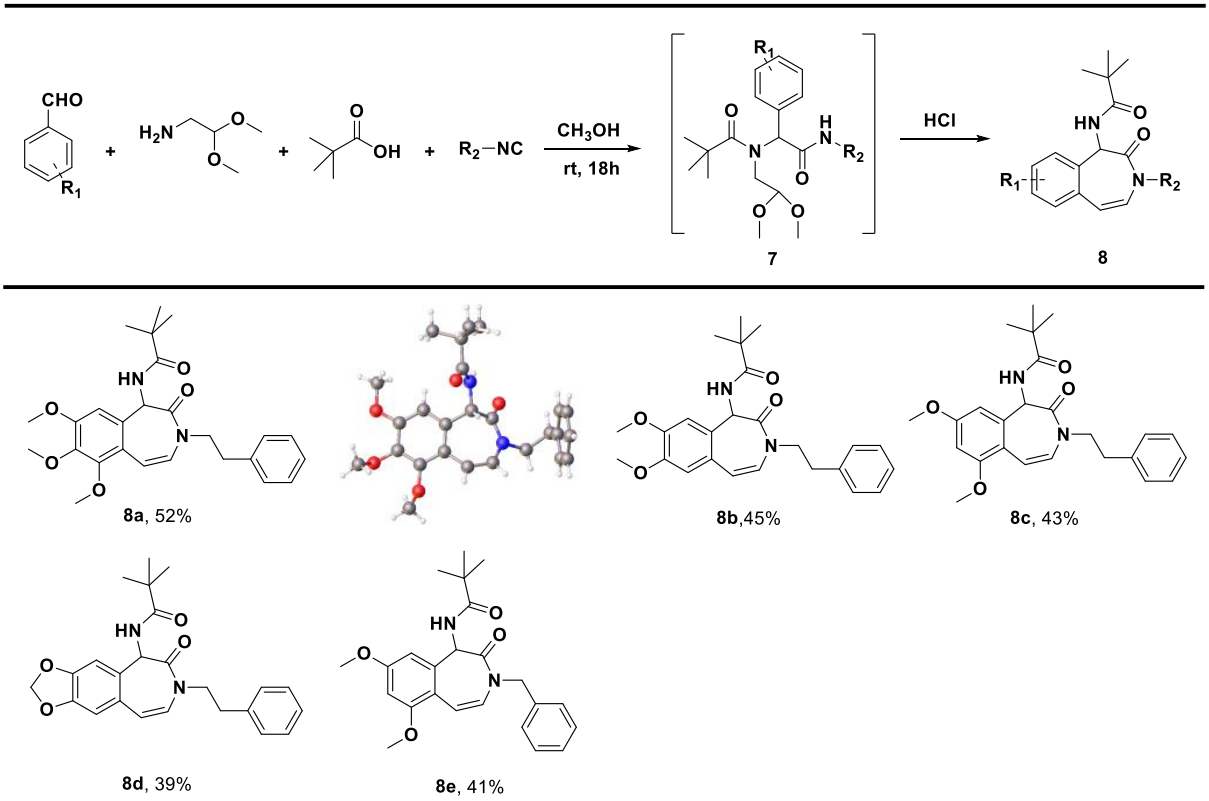
With optimal reaction conditions in hand, nine isoquinoline products **6** were synthesized by using three aldehydes, three isocyanides and eight acids (Scheme 4). Both aromatic and aliphatic isocyanides work well for this reaction. Regarding the acid moiety, all Ugi adducts obtained from aromatic acid can afford isoquinolines in good to moderate yield. Albeit in lower yields, most of the aliphatic acid also work except trimethylacetic acid, which failed to give any cyclized product. The structure of **6j** was confirmed by X-ray crystallography.

To figure out why trimethylacetic acid did not work for the Ugi/Pomeranz–Fritsch reaction, we rescreened all the acid conditions in Scheme 3. Unexpectedly, we observed the formation of the benzo[*d*]azepinone scaffold in good yield when 37% HCl diluted in dioxane was used as the acid. As a class of seven-membered *N*-heterocycles, benzo[*d*]azepinone scaffolds are also very interesting in medicinal chemistry, where they represent an important class of "privileged scaffolds". [55,56] We synthesized five compounds in 39-52% yield by changing the aldehyde moiety and isocyanide moiety as shown in Scheme 5. A single crystal X-ray analysis further confirmed the structure of **8a**.



Scheme 4. Synthesis of isoquinolines derivatives.

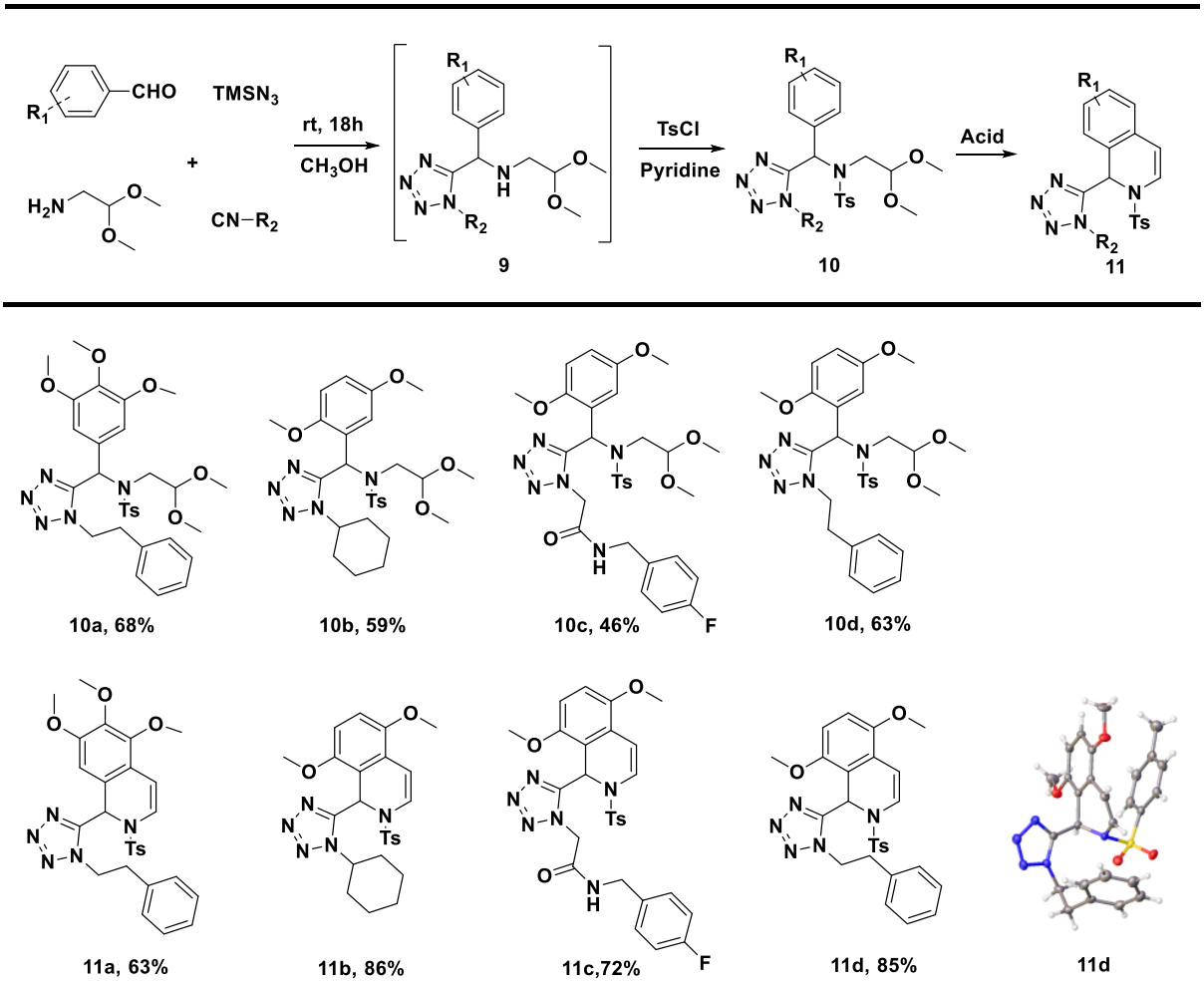
As valuable bioisosteres of carboxylic acids and cis-amide, tetrazoles are an important drug-like scaffold which exhibiting improved pharmacokinetic properties in drug discovery. Exploration of the Ugi-Azide MCR and its postcyclization have created several unique scaffolds as exemplified by ketopiperazine-tetrazoles, [57] quinoxaline-tetrazoles,[58] azepine-tetrazoles,[59,60] benzodiazepine-tetrazoles[61] and Lactam-tetrazoles.[62-64] Inspired by these methodologies, we successfully constructed the isoquinoline-tetrazoles by combining the Ugi-Azide reaction with Pomeranz-Fritsch reaction. Initially, we tried to cyclize the Ugi-azide product **9** directly in acid condition. To our surprise, however, the subsequent Pomeranz-Fritsch reaction was very sluggish and only trace amount of product was formed. In addition, variation of the acid condition and solvent did not greatly contribute to the reaction performance. We reasoned that the exposed secondary amine could interfere with the reaction and cause side reactions. Thus, we first protected the secondary amine by tosyl group in situ to obtain product **10**, which then undergoes cyclization to form the isoquinoline-tetrazoles **11**. (Scheme 6)



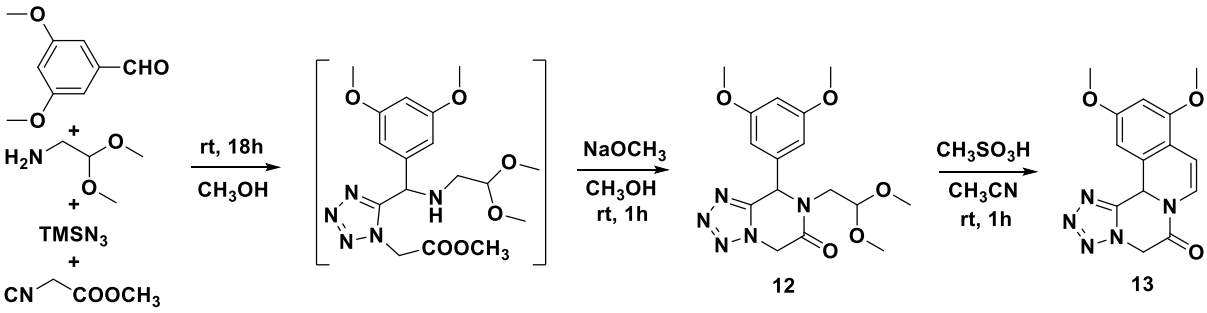
Scheme 5. Synthesis of benzo[*d*]azepinone scaffold.

As a further application, we successfully constructed an alkaloid-like tetrazole-fused tetracyclic compound by using isocyanide prepared from amino acid ester as starting material (Scheme 7). Instead of tosyl group protection, the methyl ester from isocyanide moiety will react with the exposed secondary amine in basic condition to form the tetrazolopyrazinone **12**, followed by the Pomeranz-Fritsch cyclization to afford tetracyclic product **13**.

In conclusion, we have developed straightforward methods to assemble isoquinoline derivatives and benzo[*d*]azepinone scaffold. The Ugi condensation followed by post-cyclization reactions, which is probably the most powerful tool to create structural diversity with the shortest procedure, has gained a lot of interest in the field of medicinal chemistry. Our new strategy of Ugi/Pomeranz-Fritsch reaction is expeditious and convergent access to skeletal diverse compound. Significantly, isoquinoline-tetrazoles and tetrazole-fused tetracyclic compound can also be constructed in two step with this method.



Scheme 6. Synthesis of isoquinoline-tetrazoles.



Scheme 7. Synthesis of tetracyclic product.

Experiment Procedures

General procedure A: synthesis of isoquinoline **6**

To the stirred solution of oxo-component (1 mmol, 1.0 equiv.) in methanol (1M) at room temperature, was added 2,2-dimethoxyethylamine (1 mmol, 1.0 equiv.), acid (1 mmol, 1.0 equiv.) and isocyanide (1 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature for 18 h. Solvents were removed under vacuum. Then the crude Ugi-adduct (**5**) was dissolved in 3 mL acetonitrile and methanesulfonic acid (20 mmol, 20.0 equiv.) was added. The resulting mixture was stirred at room temperature for 18 h. The reaction was diluted with dichloromethane and quenched with saturated sodium bicarbonate solution at 0-5 ℃. The resulting solution was extracted with dichloromethane (10 mL x 3). The solvents were removed under vacuum and the crude product was purified by flash column chromatography to give pure product (**6**).

General procedure B: synthesis of benzo[*d*]azepinone **8**

To the stirred solution of oxo-component (1 mmol, 1.0 equiv.) in methanol (1M) at room temperature, was added 2,2-dimethoxyethylamine (1 mmol, 1.0 equiv.), trimethylacetic acid (1 mmol, 1.0 equiv.) and isocyanide (1 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature for 18 h. Solvents were removed under vacuum. Then the crude Ugi-adduct (**7**) was dissolved in 2 mL dioxane and 2 mL 37% HCl solution was added. The resulting mixture was stirred at room temperature for 18 h. The reaction was diluted with dichloromethane and quenched with saturated sodium bicarbonate solution at 0-5 ℃. The resulting solution was extracted with dichloromethane (10 mL x 3). The solvents were removed under vacuum and the crude product was purified by flash column chromatography to give pure product (**8**).

General procedure C: synthesis of tetrazole **10**

To the stirred solution of oxo-component (2 mmol, 1.0 equiv.) in methanol (1M) at room temperature, was added 2,2-dimethoxyethylamine (2 mmol, 1.0 equiv.), isocyanide (2 mmol, 1.0 equiv.) and trimethylsilyl azide (2 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature for 18 h. Solvents were removed under vacuum. Then the crude Ugi-adduct (**9**) was dissolved in 3 mL pyridine and p-tolunene sulfonyl chloride (2.4 mmol, 1.2 equiv.) was added. The resulting mixture was stirred at room temperature for 12 h. Solvents were removed under

vacuum. The residue was dissolved in dichloromethane (8 mL) and washed by 1M HCl solution(5 mL x 3). The solvents were removed under vacuum and the crude product was purified by flash column chromatography to give pure product (**10**).

General procedure D: synthesis of isoquinoline-tetrazole **11**

To the stirred solution of tetrazole **11** (0.5 mmol, 1.0 equiv.) in dioxane (4 mL) at room temperature, was added 6 M HCl aqueous solution (1 mL). The mixture was kept under reflux for 7 h. Solvents were removed under vacuum, the crude product was dissolved in dichloromethane (8 mL), washed by saturated sodium bicarbonate solution (5 mL x 3), saturated sodium chloride solution (5 mL x 1) and dried over $MgSO_4$. The solvents were removed under vacuum and the crude product was purified by flash column chromatography to give pure product (**11**).

General procedure E: synthesis of tetrazole **12**

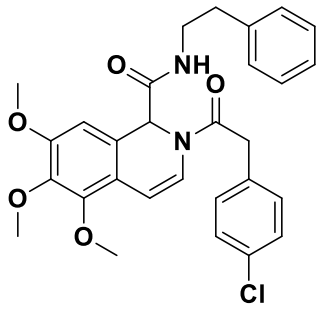
To the stirred solution of 3,5-dimethoxybenzaldehyde (3 mmol, 1.0 equiv.) in methanol (1M) at room temperature, was added 2,2-dimethoxyethylamine (3 mmol, 1.0 equiv.), Methyl isocyanoacetate (3 mmol, 1.0 equiv.) and trimethylsilyl azide (3 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature for 18 h. Then the sodium methoxide (3 mmol, 1.0 equiv.) was added. The resulting mixture was stirred at room temperature for 1 h. Solvents were removed under vacuum, the crude product was dissolved in dichloromethane (20 mL), washed by water (10 mL x 2), saturated sodium chloride solution (10 mL x 1) and dried over $MgSO_4$. The solvents were removed under vacuum and the crude product was purified by flash column chromatography to give pure product (**12**).

General procedure F: synthesis of tetracyclic product **13**

To the stirred solution of tetrazole **12** (1 mmol, 1.0 equiv.) in dioxane (2 mL) at room temperature, was added 37% HCl aqueous solution (1 mL). The resulting mixture was stirred at room temperature for 1 h. Solvents were removed under vacuum, the crude product was dissolved in dichloromethane (8 mL), washed by saturated sodium bicarbonate solution (5 mL x 3), saturated sodium chloride solution (5 mL x 1) and dried over $MgSO_4$. The solvents were removed under vacuum and the crude product was purified by flash column chromatography to give pure product (**13**).

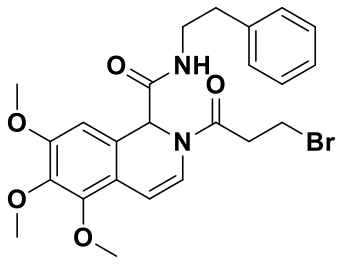
Characterization Data of Products

6a: 2-(2-(4-chlorophenyl)acetyl)-5,6,7-trimethoxy-*N*-phenethyl-1,2-dihydroisoquinoline-1-carboxamide



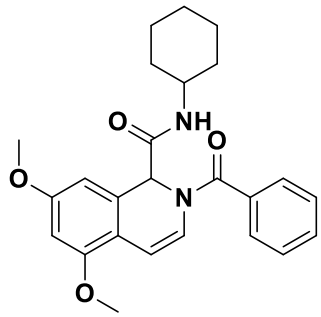
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (270 mg, 52% yield), M.P.= 160 – 161 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 5H), 7.19 – 7.15 (m, 2H), 7.06 – 7.01 (m, 2H), 6.59 – 6.55 (m, 1H), 6.51 (s, 1H), 6.19 (d, *J* = 7.8 Hz, 1H), 6.02 (s, 1H), 5.78 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 3.79 (s, 2H), 3.42 (q, *J* = 6.5 Hz, 2H), 2.78 – 2.62 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 168.6, 153.3, 148.8, 142.1, 138.6, 133.2, 132.2, 130.5, 129.0, 128.8, 128.6, 126.5, 124.1, 122.1, 117.1, 107.0, 106.4, 61.5, 61.0, 57.0, 56.2, 40.8, 39.6, 35.3; HRMS (ESI) m/z calculated for $C_{29}H_{30}ClN_2O_5$ $[M+H]^+$: 521.1838; found $[M+H]^+$: 521.1835.

6b: 2-(3-bromopropanoyl)-5,6,7-trimethoxy-*N*-phenethyl-1,2-dihydroisoquinoline-1-carboxamide



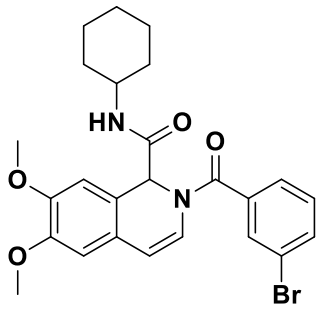
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (226 mg, 45% yield), M.P.= 153 – 155 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.17 (m, 3H), 7.09 – 7.03 (m, 2H), 6.57 – 6.50 (m, 2H), 6.23 (d, *J* = 7.8 Hz, 1H), 6.01 (s, 1H), 5.88 (t, *J* = 6.0 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.71 – 3.58 (m, 2H), 3.50 – 3.40 (m, 2H), 3.11 – 3.03 (m, 1H), 3.02 – 2.94 (m, 1H), 2.78 – 2.68 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 168.5, 153.4, 148.8, 142.1, 138.6, 128.8, 128.6, 126.5, 124.1, 121.5, 117.0, 107.1, 106.7, 61.5, 61.0, 56.9, 56.2, 40.7, 36.3, 35.2, 26.3; HRMS (ESI) m/z calculated for $C_{24}H_{28}BrN_2O_5$ $[M+H]^+$: 503.1176; found $[M+H]^+$: 503.1178.

6c: 2-benzoyl-*N*-cyclohexyl-5,7-dimethoxy-1,2-dihydroisoquinoline-1-carboxamide



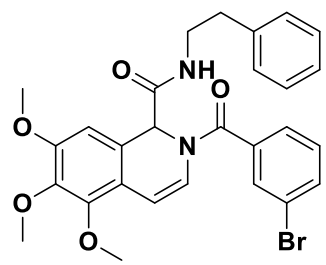
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (139 mg, 33% yield), M.P.= 241 – 243 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.56 (m, 2H), 7.52 – 7.48 (m, 1H), 7.46 – 7.41 (m, 2H), 6.54 – 6.36 (m, 3H), 6.26 (s, 1H), 6.18 (d, *J* = 7.7 Hz, 1H), 6.08 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.76 – 3.66 (m, 1H), 1.86 – 1.78 (m, 2H), 1.68 – 1.58 (m, 2H), 1.57 – 1.50 (m, 1H), 1.37 – 1.27 (m, 2H), 1.22 – 1.09 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 167.9, 160.5, 155.6, 134.0, 131.3, 130.8, 129.1, 128.6, 123.8, 113.3, 105.2, 104.1, 98.6, 58.5, 55.7, 48.4, 32.9, 32.8, 25.6, 24.6; HRMS (ESI) m/z calculated for $C_{25}H_{29}N_2O_4$ $[M+H]^+$: 421.2123; found $[M+H]^+$: 421.2122.

6d: 2-(3-bromobenzoyl)-*N*-cyclohexyl-6,7-dimethoxy-1,2-dihydroisoquinoline-1-carboxamide



The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as light yellow solid (269 mg, 54% yield), M.P.= 209 – 211 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (t, *J* = 1.8 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 6.86 (s, 1H), 6.67 (s, 1H), 6.45 (d, *J* = 7.6 Hz, 1H), 6.19 (s, 1H), 6.07 (s, 1H), 5.83 (d, *J* = 7.6 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.75 – 3.62 (m, 1H), 1.86 – 1.75 (m, 2H), 1.66 – 1.51 (m, 3H), 1.37 – 1.22 (m, 2H), 1.22 – 1.04 (m, 3H); ^{1}H NMR (500 MHz, Chloroform-*d*) ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 168.0, 149.3, 148.9, 135.8, 134.3, 131.8, 130.3, 127.4, 124.7, 123.4, 122.8, 120.8, 110.7, 110.6, 108.7, 58.1, 56.3, 56.1, 48.5, 32.8, 25.6, 24.6; HRMS (ESI) m/z calculated for $C_{25}H_{28}BrN_2O_4$ $[M+H]^+$: 499.1227; found $[M+H]^+$: 499.1225.

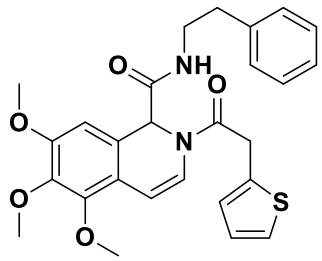
6e: *N*-benzyl-2-(3-bromopropanoyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline-1-carboxamide



The product was synthesized according to procedure A in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (336 mg, 61% yield), M.P.= 167 – 169 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 2H), 7.43 (d, *J* = 7.7

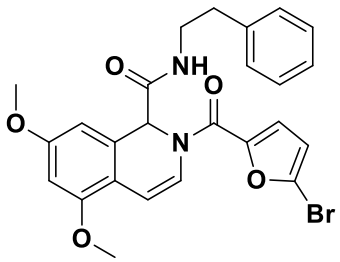
Hz, 1H), 7.33 – 7.20 (m, 4H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.58 (s, 1H), 6.35 (d, *J* = 7.8 Hz, 1H), 6.19 – 6.09 (m, 2H), 6.01 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.50 (q, *J* = 6.4 Hz, 2H), 2.77 (q, *J* = 6.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 168.1, 153.5, 149.0, 142.3, 138.8, 135.5, 134.4, 132.1, 130.1, 128.9, 128.8, 127.6, 126.7, 124.2, 124.0, 122.8, 117.5, 107.0, 105.8, 61.6, 61.1, 58.0, 56.3, 40.9, 35.4; HRMS (ESI) m/z calculated for $C_{28}H_{28}BrN_2O_5$ $[M+H]^+$: 551.1176; found $[M+H]^+$: 551.1177.

6f: 5,7-dimethoxy-*N*-phenethyl-2-(thiophene-2-carbonyl)-1,2-dihydro-isoquinoline-1-carboxamide



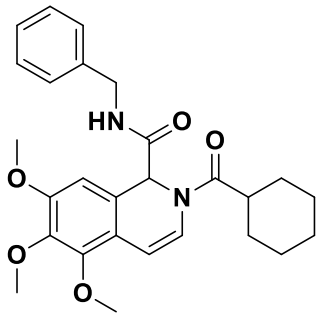
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (206 mg, 46% yield), M.P.= 187 – 189 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.58 (m, 1H), 7.56 – 7.54 (m, 1H), 7.23 – 7.18 (m, 2H), 7.18 – 7.14 (m, 1H), 7.11 – 7.05 (m, 3H), 6.73 (d, *J* = 7.2 Hz, 1H), 6.42 (d, *J* = 2.3 Hz, 1H), 6.38 (d, *J* = 2.2 Hz, 1H), 6.37 – 6.33 (m, 1H), 6.31 (d, *J* = 7.6 Hz, 1H), 5.94 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.53 – 3.41 (m, 2H), 2.84 – 2.67 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 162.6, 160.6, 155.6, 138.9, 136.3, 132.7, 131.8, 130.9, 128.9, 128.7, 127.4, 126.5, 123.3, 113.1, 106.6, 104.1, 98.7, 58.8, 55.7, 55.7, 41.0, 35.6; HRMS (ESI) m/z calculated for $C_{25}H_{25}N_2O_4S$ $[M+H]^+$: 449.1530; found $[M+H]^+$: 449.1531.

6g: 2-(5-bromofuran-2-carbonyl)-5,7-dimethoxy-*N*-phenethyl-1,2-dihydro-isoquinoline-1-carboxamide



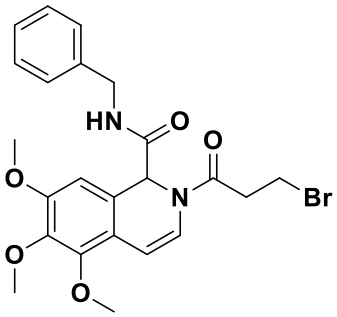
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (260 mg, 51% yield), M.P.= 142 – 144 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 2H), 7.18 – 7.14 (m, 1H), 7.05 (d, *J* = 6.8 Hz, 3H), 6.84 – 6.78 (m, 1H), 6.48 (d, *J* = 3.6 Hz, 1H), 6.41 (d, *J* = 2.3 Hz, 1H), 6.38 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 7.8 Hz, 1H), 6.25 (s, 1H), 5.94 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.45 (q, *J* = 6.6 Hz, 2H), 2.80 – 2.68 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 160.6, 157.0, 155.6, 148.1, 138.8, 130.7, 128.9, 128.6, 127.1, 126.5, 122.2, 121.2, 113.8, 112.9, 107.0, 104.1, 98.7, 58.3, 55.7, 55.7, 40.9, 35.5; HRMS (ESI) m/z calculated for $C_{25}H_{24}BrN_2O_5$ $[M+H]^+$: 511.0863; found $[M+H]^+$: 511.0864.

6h: *N*-benzyl-2-(cyclohexanecarbonyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline -1-carboxamide



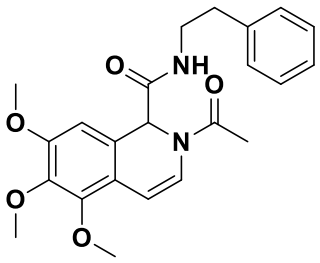
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as semi-solid (153 mg, 33% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 3H), 7.18 – 7.13 (m, 2H), 6.72 – 6.67 (m, 1H), 6.64 (s, 1H), 6.41 (t, *J* = 5.8 Hz, 1H), 6.22 (d, *J* = 7.8 Hz, 1H), 6.11 (s, 1H), 4.42 – 4.30 (m, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.68 – 2.57 (m, 1H), 1.85 – 1.64 (m, 5H), 1.55 – 1.41 (m, 2H), 1.34 – 1.18 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 169.3, 153.3, 148.8, 142.1, 138.2, 128.7, 127.5, 127.5, 124.5, 122.1, 117.5, 107.2, 105.8, 61.6, 61.1, 57.0, 56.3, 43.6, 41.0, 29.1, 25.8; HRMS (ESI) m/z calculated for $C_{27}H_{33}N_2O_5$ $[M+H]^+$: 465.2384; found $[M+H]^+$: 465.2386.

6i: *N*-benzyl-2-(3-bromopropanoyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline-1-carboxamide



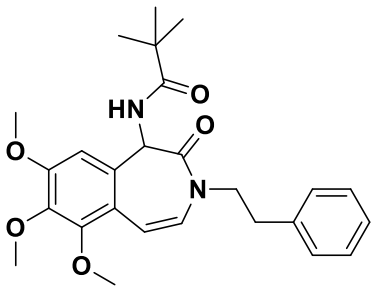
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (210 mg, 43% yield), M.P.= 195 – 197 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 3H), 7.16 – 7.13 (m, 2H), 6.66 (s, 1H), 6.66 – 6.63 (m, 1H), 6.33 (t, *J* = 5.8 Hz, 1H), 6.28 (d, *J* = 7.8 Hz, 1H), 6.12 (s, 1H), 4.46 – 4.29 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.73 – 3.61 (m, 2H), 3.25 – 3.12 (m, 1H), 3.07 – 2.94 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 168.7, 153.6, 149.0, 142.2, 137.9, 128.8, 127.6, 127.6, 124.2, 121.5, 117.1, 107.3, 107.0, 61.6, 61.1, 57.2, 56.4, 43.8, 36.4, 26.5; HRMS (ESI) m/z calculated for $C_{23}H_{26}BrN_2O_5$ $[M+H]^+$: 489.1020; found $[M+H]^+$: 489.1020.

6j: 2-acetyl-5,6,7-trimethoxy-*N*-phenethyl-1,2-dihydroisoquinoline-1-carboxamide



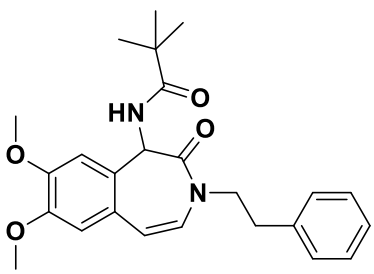
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (69 mg, 16% yield), M.P.= 108 – 110 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.27 (m, 2H), 7.23 – 7.19 (m, 1H), 7.08 – 7.04 (m, 2H), 6.56 (s, 1H), 6.52 (d, *J* = 7.9 Hz, 1H), 6.18 (d, *J* = 7.8 Hz, 1H), 6.02 (s, 1H), 5.95 (t, *J* = 6.0 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.49 – 3.38 (m, 2H), 2.79 – 2.66 (m, 3H), 2.21 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 168.9, 153.0, 148.5, 141.8, 138.6, 128.6, 128.4, 126.3, 124.0, 122.9, 117.0, 107.0, 105.1, 61.3, 60.8, 56.7, 56.0, 40.6, 35.1, 21.2; HRMS (ESI) m/z calculated for $C_{23}H_{26}N_2O_5Na$ $[M+Na]^+$: 433.1733; found $[M+Na]^+$: 433.1728.

8a: *N*-(6,7,8-trimethoxy-2-oxo-3-phenethyl-2,3-dihydro-1*H*-benzo[*d*]azepin-1-yl) pivalamide



The product was synthesized according to procedure **B** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (235 mg, 52% yield), M.P.= 111 – 112 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 6.1 Hz, 1H), 7.19 – 7.09 (m, 3H), 7.05 – 6.97 (m, 2H), 6.69 (d, *J* = 9.0 Hz, 1H), 6.49 (s, 1H), 6.14 (d, *J* = 9.1 Hz, 1H), 4.95 (d, *J* = 6.0 Hz, 1H), 4.14 – 3.98 (m, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.60 – 3.46 (m, 1H), 2.83 – 2.70 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 165.8, 155.0, 150.2, 140.9, 137.9, 130.3, 128.8, 128.5, 127.0, 126.5, 118.8, 114.7, 101.2, 61.2, 60.9, 55.7, 54.0, 49.8, 39.0, 34.6, 27.7; HRMS (ESI) m/z calculated for $C_{26}H_{33}N_2O_5$ $[M+H]^+$: 453.2384; found $[M+H]^+$: 453.2382.

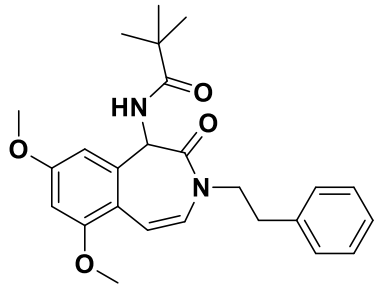
8b: *N*-(7,8-dimethoxy-2-oxo-3-phenethyl-2,3-dihydro-1*H*-benzo[*d*]azepin-1-yl) pivalamide



The product was synthesized according to procedure **B** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as semi-solid (190 mg, 45% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 5.9 Hz, 1H), 7.18 – 7.11 (m, 3H), 7.03 – 6.92 (m, 2H), 6.69 (d, *J* = 10.7 Hz,

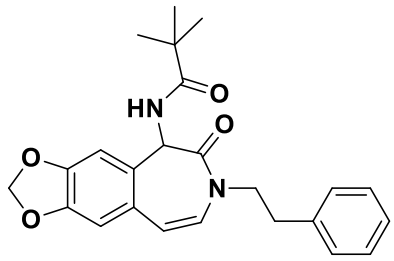
2H), 6.43 (d, *J* = 8.9 Hz, 1H), 6.07 (d, *J* = 8.9 Hz, 1H), 4.95 (d, *J* = 6.0 Hz, 1H), 4.16 – 4.03 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.56 – 3.43 (m, 1H), 2.84 – 2.68 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 166.0, 150.6, 148.3, 138.1, 128.9, 128.5, 127.2, 126.9, 126.5, 124.6, 118.8, 110.0, 105.4, 56.2, 55.8, 53.9, 50.2, 39.1, 34.7, 27.8; HRMS (ESI) m/z calculated for $C_{25}H_{31}N_2O_4$ $[M+H]^+$: 423.2278; found $[M+H]^+$: 423.2278.

8c: *N*-(6,8-dimethoxy-2-oxo-3-phenethyl-2,3-dihydro-1*H*-benzo[*d*]azepin-1-yl) pivalamide



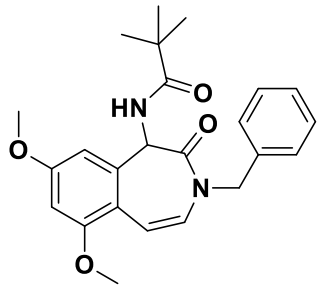
The product was synthesized according to procedure **B** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (181 mg, 43% yield), M.P.= 156 – 158 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 6.2 Hz, 1H), 7.19 – 7.12 (m, 3H), 7.05 – 6.96 (m, 2H), 6.69 (d, *J* = 9.0 Hz, 1H), 6.40 (d, *J* = 2.2 Hz, 1H), 6.33 (d, *J* = 2.1 Hz, 1H), 6.09 (d, *J* = 9.0 Hz, 1H), 4.99 (d, *J* = 6.2 Hz, 1H), 4.09 – 3.99 (m, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.56 – 3.44 (m, 1H), 2.81 – 2.72 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.7, 165.8, 162.1, 157.5, 138.1, 137.0, 128.9, 128.5, 126.5, 114.9, 114.4, 106.0, 98.3, 97.5, 55.7, 55.4, 54.3, 49.9, 39.1, 34.6, 27.7; HRMS (ESI) m/z calculated for $C_{25}H_{31}N_2O_4$ $[M+H]^+$: 423.2278; found $[M+H]^+$: 423.2279.

8d: *N*-(6-oxo-7-phenethyl-6,7-dihydro-5*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*d*] azepin-5-yl)pivalamide



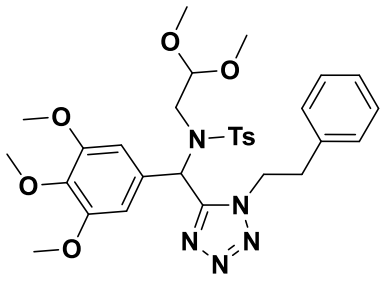
The product was synthesized according to procedure **B** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (159 mg, 39% yield), M.P.= 142 – 143 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.18 (m, 3H), 7.12 – 7.07 (m, 2H), 6.79 (d, *J* = 1.3 Hz, 1H), 6.73 (s, 2H), 6.39 (s, 1H), 6.09 (s, 1H), 5.95 – 5.90 (m, 2H), 5.29 (d, *J* = 5.9 Hz, 1H), 3.86 – 3.71 (m, 2H), 2.88 (t, *J* = 7.0 Hz, 2H), 1.31 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 164.7, 148.0, 147.5, 138.1, 129.1, 128.7, 126.8, 119.9, 113.6, 110.3, 108.4, 107.3, 101.2, 59.1, 48.1, 39.7, 34.7, 28.0, 27.9; HRMS (ESI) m/z calculated for $C_{24}H_{27}N_2O_4$ $[M+H]^+$: 407,1965; found $[M+H]^+$: 407,1968.

8e: *N*-(3-benzyl-6,8-dimethoxy-2-oxo-2,3-dihydro-1*H*-benzo[d]azepin-1-yl) pivalamide



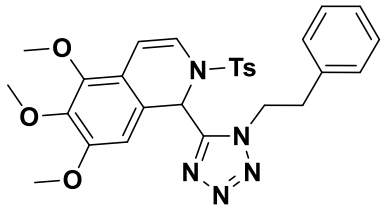
The product was synthesized according to procedure **B** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (176 mg, 41% yield), M.P.= 139 – 141 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 6.3 Hz, 1H), 7.29 – 7.21 (m, 3H), 7.12 – 7.08 (m, 2H), 6.75 (d, *J* = 9.0 Hz, 1H), 6.40 – 6.37 (m, 2H), 6.21 (d, *J* = 9.0 Hz, 1H), 5.12 (d, *J* = 6.2 Hz, 1H), 4.85 – 4.65 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 166.3, 162.1, 157.6, 137.0, 136.1, 128.8, 127.7, 127.5, 126.0, 115.0, 114.4, 98.5, 97.7, 55.9, 55.3, 54.3, 51.0, 39.1, 27.8; HRMS (ESI) m/z calculated for $C_{24}H_{28}N_2O_4Na$ $[M+Na]^+$: 431.1941; found $[M+Na]^+$: 431.1941.

10a: *N*-(2,2-dimethoxyethyl)-4-methyl-*N*-((1-phenethyl-1*H*-tetrazol-5-yl)(3,4,5-trimethoxyphenyl)methyl)benzenesulfonamide



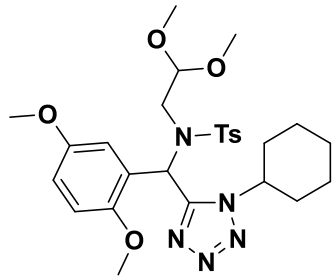
The product was synthesized according to procedure **C** in 2 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as semi-solid (830 mg, 68% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.23 – 7.12 (m, 6H), 7.09 – 7.05 (m, 1H), 6.11 (s, 1H), 5.96 (s, 2H), 4.61 (dd, *J* = 8.0, 6.0 Hz, 2H), 4.22 (dd, *J* = 6.4, 4.0 Hz, 1H), 3.78 (s, 3H), 3.60 (s, 6H), 3.58 – 3.53 (m, 1H), 3.47 – 3.41 (m, 1H), 3.21 (s, 3H), 3.27 – 3.15 (m, 2H), 3.08 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 152.7, 144.3, 138.4, 136.2, 135.6, 129.6, 128.9, 128.7, 127.6, 127.4, 105.8, 105.7, 103.2, 103.1, 60.9, 60.9, 56.1, 55.0, 54.9, 54.5, 53.9, 48.8, 47.7, 35.8, 21.6; HRMS (ESI) m/z calculated for $C_{30}H_{37}N_5O_7SNa$ $[M+Na]^+$: 634.2306; found $[M+Na]^+$: 634.2306.

11a: 5,6,7-trimethoxy-1-(1-phenethyl-1*H*-tetrazol-5-yl)-2-tosyl-1,2-dihydro-isoquinoline



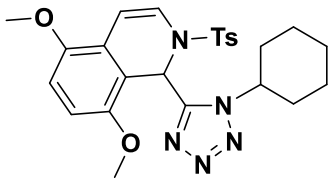
The product was synthesized according to procedure **D** in 0.5 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (172 mg, 63% yield), M.P.= 180 – 182 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.33 (m, 2H), 7.33 – 7.30 (m, 1H), 7.23 – 7.19 (m, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.48 (d, *J* = 7.3 Hz, 1H), 6.29 – 6.25 (m, 1H), 5.80 (s, 1H), 5.69 (s, 1H), 5.03 – 4.94 (m, 1H), 4.91 – 4.83 (m, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.64 (s, 3H), 3.35 – 3.18 (m, 2H), 2.25 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.87, 153.11, 148.99, 144.56, 142.18, 136.94, 133.48, 129.72, 129.14, 128.91, 127.26, 127.12, 121.39, 121.10, 116.90, 114.48, 105.89, 61.29, 61.00, 56.43, 50.94, 48.85, 36.59, 21.57. HRMS (ESI) m/z calculated for $C_{28}H_{30}N_5O_5S$ $[M+H]^+$: 548,1962; found $[M+H]^+$: 548,1973.

10b: *N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)(2,5-dimethoxyphenyl)methyl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide



The product was synthesized according to procedure **C** in 2 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (658 mg, 59% yield), M.P.= 146 – 148 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.80 (s, 1H), 6.75 – 6.72 (m, 2H), 6.25 (d, *J* = 2.5 Hz, 1H), 4.36 – 4.28 (m, 2H), 3.72 – 3.64 (m, 1H), 3.60 – 3.56 (m, 4H), 3.53 (s, 3H), 3.09 (s, 3H), 3.04 (s, 3H), 2.36 (s, 3H), 2.23 – 2.16 (m, 1H), 2.13 – 2.04 (m, 1H), 2.01 – 1.95 (m, 1H), 1.91 – 1.82 (m, 3H), 1.77 – 1.69 (m, 1H), 1.51 – 1.42 (m, 1H), 1.41 – 1.27 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 152.8, 150.8, 143.9, 136.2, 129.4, 127.7, 123.6, 114.9, 111.9, 103.4, 57.9, 56.0, 55.6, 54.5, 53.4, 50.6, 48.3, 33.0, 32.3, 25.4, 21.6; HRMS (ESI) m/z calculated for $C_{27}H_{27}N_5O_4SNa$ $[M+Na]^+$: 582.2357; found $[M+Na]^+$: 582.2354.

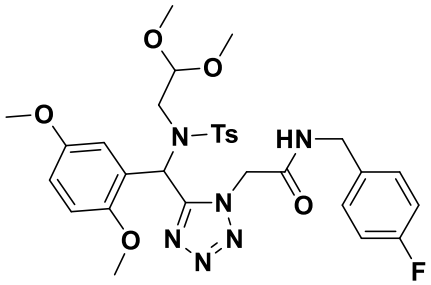
11b: 1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-5,8-dimethoxy-2-tosyl-1,2-dihydro-isoquinoline



The product was synthesized according to procedure **D** in 0.5 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (213 mg, 86% yield), M.P.= 141 – 143 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ7.52 – 7.49 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.88 (s, 1H),

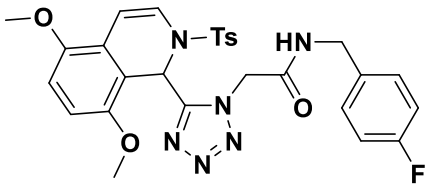
6.66 – 6.59 (m, 3H), 6.49 – 6.46 (m, 1H), 4.99 – 4.90 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 2.28 (s, 3H), 2.23 – 2.16 (m, 1H), 2.10 – 1.95 (m, 5H), 1.85 – 1.77 (m, 1H), 1.65 – 1.53 (m, 2H), 1.42 – 1.31 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.8, 148.7, 148.5, 144.3, 134.8, 129.4, 126.9, 123.0, 120.1, 116.0, 112.5, 111.3, 110.4, 58.1, 56.2, 55.9, 45.1, 33.3, 33.2, 25.7, 25.4, 25.1, 21.6; HRMS (ESI) m/z calculated for $C_{25}H_{29}N_5O_4SNa$ $[M+Na]^+$: 518.1833; found $[M+Na]^+$: 518.1835.

10c: 2-(5-(((*N*-(2,2-dimethoxyethyl)-4-methylphenyl)sulfonamido)(2,5-dimethoxyphenyl)methyl)-1*H*-tetrazol-1-yl)-*N*-(4-fluorobenzyl)acetamide



The product was synthesized according to procedure **C** in 2 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (786 mg, 46% yield), M.P.= 148 – 150 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.23 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.99 – 6.92 (m, 2H), 6.76 – 6.71 (m, 2H), 6.70 – 6.66 (m, 2H), 6.17 (d, *J* = 2.9 Hz, 1H), 5.17 (d, *J* = 16.6 Hz, 1H), 5.07 (d, *J* = 16.6 Hz, 1H), 4.53 – 4.38 (m, 2H), 4.31 (m, 1H), 3.59 – 3.55 (m, 2H), 3.53 (s, 3H), 3.42 (s, 3H), 3.09 (s, 3H), 2.98 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 163.3, 161.4, 154.5, 153.4, 150.6, 144.3, 135.8, 133.4, 129.8, 129.8, 129.6, 127.6, 122.3, 115.7, 114.7, 111.9, 103.2, 55.9, 55.5, 54.5, 53.7, 50.9, 50.8, 49.9, 48.1, 43.3, 21.6; HRMS (ESI) m/z calculated for $C_{30}H_{35}FN_6O_7SNa$ $[M+Na]^+$: 665.2164; found $[M+Na]^+$: 665.2164.

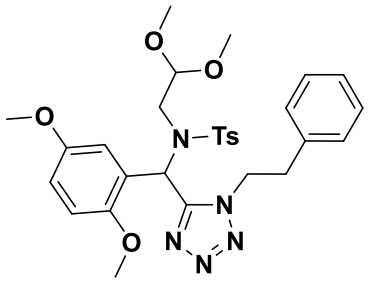
11c: 2-(5-(5,8-dimethoxy-2-tosyl-1,2-dihydroisoquinolin-1-yl)-1*H*-tetrazol-1-yl)-*N*-(4-fluorobenzyl)acetamide



The product was synthesized according to procedure **D** in 0.5 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (208 mg, 72% yield), M.P.= 106 – 108 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.9 Hz, 2H), 7.32 – 7.27 (m, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 7.00 (t, *J* = 8.4 Hz, 2H), 6.76 (s, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.61 – 6.54 (m, 2H), 6.49 (d, *J* = 7.6 Hz, 1H), 6.44 (t, *J* = 5.8 Hz, 1H), 5.40 (s, 2H), 4.60 – 4.52 (m, 1H), 4.45 – 4.38 (m, 1H), 3.71 (s, 3H), 3.62 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.1, 163.4, 161.4, 153.8, 148.7, 148.6, 144.7, 134.4, 133.3, 129.9, 129.6, 126.9, 123.0, 119.7, 115.8, 115.6, 115.2, 111.6, 111.3, 110.7,

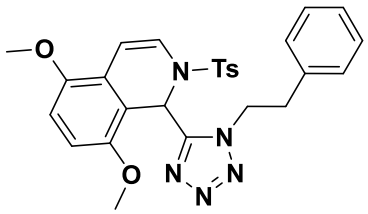
56.1, 56.1, 50.2, 45.4, 43.4; HRMS (ESI) m/z calculated for $C_{28}H_{27}FN_6O_5SNa$ $[M+Na]^+$: 601,1639; found $[M+Na]^+$: 601,1637.

10d: *N*-(2,2-dimethoxyethyl)-*N*-((2,5-dimethoxyphenyl)(1-phenethyl-1*H*-tetrazol-5-yl)methyl)-4-methylbenzenesulfonamide



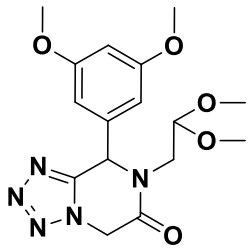
The product was synthesized according to procedure **C** in 2 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as light yellow solid (732 mg, 63% yield), M.P.= 143 – 144 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H), 7.31 – 7.19 (m, 5H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.85 (s, 1H), 6.78 – 6.71 (m, 2H), 6.28 (d, *J* = 2.7 Hz, 1H), 4.65 – 4.52 (m, 2H), 4.31 (t, *J* = 5.2 Hz, 1H), 3.60 (d, *J* = 5.3 Hz, 2H), 3.57 (s, 3H), 3.54 (s, 3H), 3.26 – 3.18 (m, 2H), 3.09 (s, 3H), 3.07 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 153.4, 150.8, 143.9, 136.5, 136.1, 129.4, 128.9, 127.7, 127.3, 123.0, 115.0, 114.7, 111.8, 103.5, 56.0, 55.6, 54.9, 53.5, 50.3, 50.2, 48.6, 48.2, 35.7, 21.6; HRMS (ESI) m/z calculated for $C_{29}H_{36}N_5O_6S$ $[M+H]^+$: 582,2381; found $[M+H]^+$: 582,2387.

11d: 5,8-dimethoxy-1-(1-phenethyl-1*H*-tetrazol-5-yl)-2-tosyl-1,2-dihydro-isoquinoline



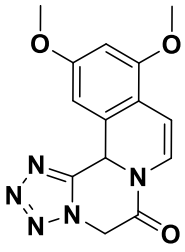
The product was synthesized according to procedure **D** in 0.5 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (219 mg, 85% yield), M.P.= 155 – 157 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.34 (m, 4H), 7.32 – 7.27 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 1.2 Hz, 1H), 6.67 – 6.57 (m, 3H), 6.44 (m, 1H), 4.99 – 4.79 (m, 2H), 3.71 (s, 3H), 3.65 (s, 3H), 3.37 (t, *J* = 8.1 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 148.7, 148.6, 144.4, 136.8, 134.6, 129.4, 129.2, 129.0, 127.2, 126.9, 122.9, 119.9, 115.7, 112.9, 111.3, 110.5, 56.1, 55.9, 49.0, 45.2, 36.1, 21.6; HRMS (ESI) m/z calculated for $C_{27}H_{27}N_5O_4SNa$ $[M+Na]^+$: 540.1676; found $[M+Na]^+$: 540.1677.

12: 7-(2,2-dimethoxyethyl)-8-(3,5-dimethoxyphenyl)-7,8-dihydrotetrazolo [1,5-a] pyrazin-6(5*H*)-one



The product was synthesized according to procedure **E** in 3 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as colorless oil (675 mg, 62% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 – 6.39 (m, 3H), 6.33 (s, 1H), 5.37 – 5.27 (m, 1H), 5.17 – 5.07 (m, 1H), 4.54 – 4.49 (m, 1H), 4.31 – 4.26 (m, 1H), 3.77 (s, 6H), 3.40 (s, 3H), 3.38 (s, 3H), 2.93 – 2.85 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.9, 161.5, 137.4, 104.9, 103.1, 100.9, 57.8, 55.8, 55.7, 55.7, 55.6, 55.0, 48.0, 47.0; HRMS (ESI) m/z calculated for $C_{16}H_{22}N_5O_5$ $[M+H]^+$: 364,1616; found $[M+H]^+$: 364,1617.

13: 10, 12-dimethoxy-13b*H*-tetrazolo[5',1':3,4]pyrazino[2,1-a]isoquinolin-6(5*H*)-one



The product was synthesized according to procedure **F** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (276 mg, 92% yield), M.P.= 185 – 186 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 2.1 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H), 6.08 – 6.05 (m, 1H), 5.31 – 5.18 (m, 2H), 3.86 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.50, 157.76, 156.12, 146.79, 129.14, 121.68, 113.28, 112.20, 101.52, 99.14, 55.92, 55.84, 53.40, 47.70; HRMS (ESI) m/z calculated for $C_{14}H_{14}N_5O_3$ $[M+H]^+$: 300,1091; found $[M+H]^+$: 300,1095.

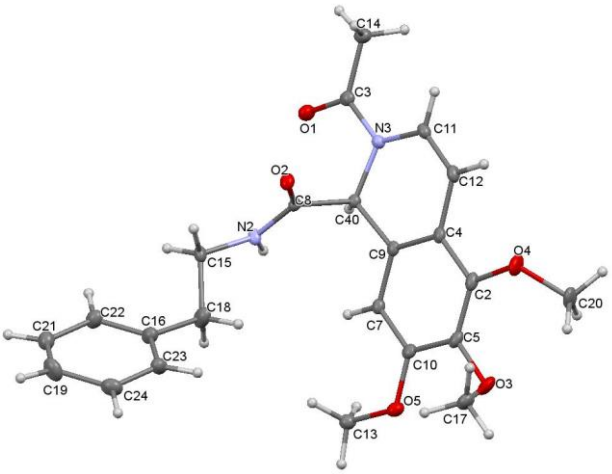
Crystal structure determination

X-ray diffraction data for single crystals of compounds **6j**, **8a** and **11d** was collected using SuperNova (Rigaku - Oxford Diffraction) four circle diffractometer with a mirror monochromator and a microfocus MoKα radiation source (λ = 0.71073 Å) which was used for monocrystals of **6j**, **8a** and **11d**. Additionally, the diffractometer was equipped with a CryoJet HT cryostat system (Oxford Instruments) allowing low temperature experiments performed at 130(2) K for all but **6j**, for which the experiment temperature was set at 120(2) K. The obtained data sets were processed with CrysAlisPro software.[65] The phase problem was solved with direct methods using SIR2004 [66] or SUPERFLIP.[67] Parameters of obtained models were refined by full-matrix least-squares on F^2 using SHELXL-2014/6 .[68] Calculations were performed using WinGX integrated system (ver. 2014.1).[69] Figure was prepared with Mercury 3.7 software.[70]

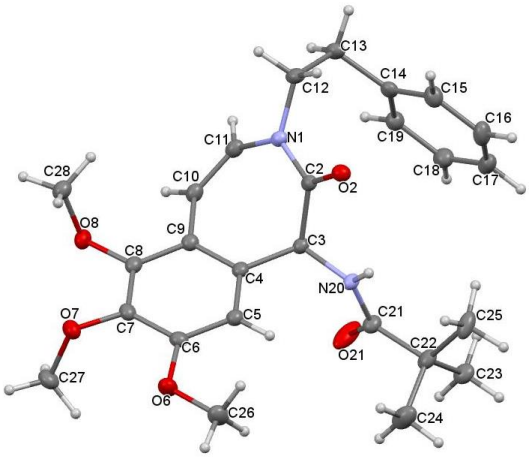
All non-hydrogen atoms were refined anisotropically. All hydrogen atoms attached to carbon atoms were positioned with the idealised geometry and refined using the riding model with the isotropic displacement parameter $U_{iso}[H] = 1.2$ (or 1.5 (methyl groups only)) $U_{eq}[C]$. Hydrogen atoms bound to nitrogen atoms were positioned on the difference Fourier map and were refined with no restrains on the isotropic displacement parameters. Crystal data and structure refinement results for presented crystal structures are shown in Table S1. The molecular geometry observed in crystal structures are shown in Figure S1.

In the asymmetric unit of **8a**, two independent molecules are observed with slightly different conformation of the phenethyl group. In the case of structure **6j**, a conformational disorder within the phenyl ring of the phenethyl group is observed, with refined site occupancies being equal for both alternative conformers.

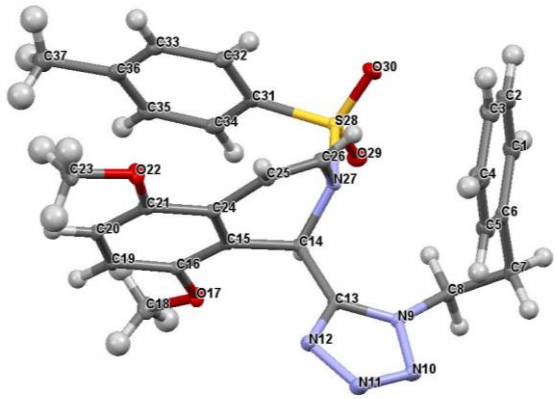
Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos.: CCDC1828772 (**11d**), CCDC1827938 (**8a**), CCDC 1573261 (**6j**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).



6j



8a



11d

Figure S1. Molecular geometry observed in the crystal structures of compounds **6j**, **8a** and **11d** showing the atom labelling scheme (here asymmetric units are presented except for **8a**, for which two independent molecules are observed in the asymmetric unit). Conformational disorder within the phenyl ring of the phenethyl group is observed in structure **6j**, with equal site occupancy (50:50; here only one of two alternative conformers are presented). Displacement ellipsoids of non-hydrogen atoms are drawn at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius.

	6j	**8a**	**11d**
Empirical moiety formula	C_{23} H_{26} N_2 O_5	2x(C_{26} H_{32} N_2 O_5)	C_{27} H_{27} N_5 O_4 S
Formula weight [g/mol]	410.46	905.07	517.6
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/a$	$P2_1/c$	$P2_1/c$
Unite cell dimensions	a = 20.7080(9) Å b = 4.8520(2) Å c = 21.0870(9) Å β=107.641(4) °	a = 16.3314(3) Å b = 13.1107(2) Å c = 23.2812(4) Å β=99.730(2) °	a =8.7940(2) b = 22.5527(7) c = 12.6632(4) β=97.367(3) °
Volume [$Å^3$]	2019.09(15)	4913.17(15)	2490.73(13)
Z	4	8 (Z'=2)	4
D_{calc} [Mg/m^3]	1.350	1.224	1.380
μ [mm^{-1}]	0.096	0.085	0.175
F(000)	872	1936	1088
Crystal size [mm^3]	0.2 x 0.2 x 0.05	0.5 x 0.4 x 0.2	0.2 x 0.15 x 0.10
Θ range	3.04 °to 28.62 °	2.97 °to 28.65 °	2.95 °to 28.52 °
Index ranges	-26 ≤ h ≤ 27, -6 ≤ k ≤ 6, -27 ≤ l ≤ 27	-16 ≤ h ≤ 21, -17 ≤ k ≤ 15, -29 ≤ l ≤ 29	-11 ≤ h ≤ 11, -28 ≤ k ≤ 29, -15 ≤ l ≤ 15
Refl. collected	16348	47242	11324
Independent reflections	4788 [R(int) = 0.0417]	11810 [R(int) = 0.0373]	5677 [R(int) = 0.0282]
Completeness [%] to Θ	99.8 (Θ 25.2°)	99.8 (Θ 25.2°)	99.8 (Θ 26.3°)
Absorption correction	Multi-scan	Multi-scan	Multi-scan
Tmin. and Tmax.	0.771 and 1.000	0.593 and 1.000	0.567 and 1.000
Data/ restraints/parameters	4788 / 6 / 314	11810 / 0 / 615	5677 / 0 / 338

GooF on F2	1.034	1.034	1.042
Final R indices [I>2sigma(I)]	R1= 0.0478, wR2= 0.1067	R1= 0.0531, wR2= 0.1174	R1= 0.0407, wR2= 0.0957
R indices (all data)	R1= 0.0705, wR2= 0.1190	R1= 0.0881, wR2= 0.1404	R1= 0.0548, wR2= 0.1054
$\Delta\rho_{max}$, $\Delta\rho_{min}$ [e $\cdot$Å^{-3}]	0.33 and -0.24	0.57 and -0.22	0.38 and -0.42

Table S1. Crystal data and structure refinement results for compounds **6j**, **8a** and **11d**.

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